Drug Class Review on Macrolides

Final Report

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The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Table of Contents

LISTING OF IN-TEXT TABLES

EVIDENCE TABLES are available on request as an addendum to this report.

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INTRODUCTION

The macrolide antibiotic class is based upon the structure of erythromycin, the prototype natural macrolide isolated from *Streptomyces erythreus*.[1] The systemic macrolides available in the United States are erythromycin and the two advanced macrolides - clarithromycin and azithromycin. Azithromycin, although technically an azalide, is commonly included in the macrolide class, and will not be differentiated in this report. Any macrolides available only outside of the United States (dirithromycin, roxithromycin, etc.) were not included in this report. Finally, telithromycin, which is the only available ketolide (an antibiotic that is structurally similar to but considered to be distinct from the macrolides) was also not included in this report. Table 1 provides a detailed description of these drugs.

Widely used, all three macrolides are represented among the top 300 drugs prescribed for outpatients in the United States in 2004.[2] Although used in a variety of infections, macrolides are most commonly used in respiratory infections.

Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit.[3] The advanced macrolides have improved binding to the ribosomes compared to erythromycin. Active efflux of antibiotics out of the cell, mediated by *mef* genes, and ribosomal methylation of the target site, mediated by *erm* genes, are the most clinically important resistance mechanisms. Organisms containing the *mef* gene commonly express low-level resistance that can often be overcome with larger doses of the antibiotic. In contrast, *erm* containing organisms (designated with the phenotype MLS_B) often express high level resistance rendering macrolides clinically ineffective.

Macrolides have activity against many classes of bacteria, but have only sporadic activity within each of these groups. The macrolides are particularly noted for their microbiologic activity against respiratory pathogens (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella* spp.), including intracellular pathogens (*Legionella spp, Chlamydia pneumoniae, Mycoplasma pneumoniae*). The macrolides attain high intracellular concentrations and are active against *Legionella* spp, *Chlamydia* spp, and *Mycoplasma pneumoniae*.[4-7] In addition, azithromycin and clarithromycin have activity against some strains of atypical non-tuberculosis mycobacteria including *Mycobacterium avium* complex. [8-10]

The macrolides lack significant microbiologic activity against most gram negative aerobic bacteria, but do have activity against two key respiratory pathogens: *H. influenzae* and *M. catarrhalis*. Of note, however, azithromycin and clarithromycin possess superior in vitro activity against *H. influenzae* when compared to erythromycin.[5, 11-13] Erythromycin displays minimal activity against this common respiratory pathogen, while the advanced macrolides have considerable activity.

Among gram positive aerobic bacteria, erythromycin possesses reasonable activity against most Streptococci, including *S. pneumoniae*, and modest activity against methicillin-susceptible *Staphylococcus aureus*.[14-16] The advanced macrolides (azithromycin, clarithromycin) have similar activity against *S. pneumoniae*. The utility of the macrolides against pneumococci are hampered by increasing resistance, commonly coupled with penicillin resistance. A 1999-2000 study from 25 countries reported 31% worldwide macrolide resistance.[17] The predominant worldwide resistance mechanism is *erm*(B) mediated high level resistance (56.2%), but there is considerable international variability. Resistant North American isolates most commonly contain low level *mef*(A) resistance, while most European and Far East countries report higher levels of *erm*(B) containing pathogens. Resistance mechanisms are important, as low level

resistance may possibly be overcome with conventional dosing of the macrolides.[3] The prevalence of these variable mechanisms of resistance may be important when comparing studies across countries and over time. Pneumococcal resistance to one macrolide commonly infers resistance to all members of the class.

Table 1. Macrolide Drug Indications and Dosing

Generic name Common trade name(s)	Labeled indications and dosing - adult	Labeled indications and dosing - children
Erythromycin ERYC® Ery-tab® Erythromycin Base Filmtab® PCE Dispertab® etc.)	●**Bacterial lower respiratory infection**, Caused by *S. pyogenes* or *S. pneumonia*: (base) 250 mg every 6 hr or 500 mg every 12 hr; max 4 g/day; (delayed-release base) 250 mg every 6 hr or 333 mg every 8 hr or 500 mg every 12 hr; max 4 g/day, depending on type and severity of infection ●**Infection due to *Mycoplasma pneumoniae***: (base) 250 mg every 6 hr or 500 mg every 12 hr; max 4 g/day; (delayed-release base) 250 mg every 6 hr or 333 mg every 8 hr or 500 mg every 12 hr; max 4 g/day, depending on type and severity of infection	●**Bacterial lower respiratory infection**, caused by *S. pyogenes* or *S. pneumonia*: (base) 30 to 50 mg/kg/day divided every 6-8 hr; max 2 g/day as base, depending on type and severity of infection ●**Infection due to *Mycoplasma pneumoniae***: (base) 30 to 50 mg/kg/day divided every 6-8 hr; max 2 g/day as base, depending on type and severity of infection
Clarithromycin Biaxin® Biaxin XL®	●**Acute exacerbation of chronic bronchitis** - Bacterial infectious disease: 250-500 mg twice daily for 7-14 days; extended-release tablets, 1000 mg once daily for 7 days ●**Community acquired pneumonia**: 250 mg twice daily for 7-14 days; extended-release tablets, 1000 mg once daily for 7 days ●**Disseminated infection due to Mycobacterium avium-intracellulare group**: 500 mg twice daily in combination with other antimycobacterial medications ●**Maxillary sinusitis, acute**: 500 mg twice daily for 14 days; extended-release tablets, 1000 mg once daily for 14 days ●**Pharyngitis**: 250 mg twice daily for 10 days	●**Acute otitis media**: 15 mg/kg/day (divided every 12 hours) for 10 days, max 1g/day ●**Community acquired pneumonia**: 15 mg/kg/day (divided every 12 hours) for 10 days, max 1g/day ●**Disseminated infection due to Mycobacterium avium-intracellulare group**: 7.5 mg/kg twice daily (MAX 500 mg twice daily) in combination with other antimycobacterial medications; Prophylaxis - HIV infection: 7.5 mg/kg twice daily (max 500 mg twice daily) ●**Maxillary sinusitis, acute**: 15 mg/kg/day (divided every 12 hours) for 10 days, max 1g/day ●**Pharyngitis**: 15 mg/kg/day (divided every 12 hours) for 10 days, max 1g/day

Table 1. Macrolide Drug Indications and Dosing(continued)

Generic name Common trade name(s)	Labeled indications and dosing - adult	Labeled indications and dosing - children
Azithromycin Zithromax® ZMAX®	●**Acute exacerbation of chronic bronchitis:** 500 mg/day for 3 days OR 500 mg on day 1, 250 mg/day on days 2-5 ●**Bacterial sinusitis, acute (Mild to Moderate**): tablets: 500 mg/day for 3 days; extended-release oral suspension: single 2 gram dose ●**Community acquired pneumonia (Mild to Moderate)**: tablets: 500 mg on day 1, 250 mg/day on days 2-5; extended-release oral suspension: a single 2 gram dose; 500 mg IV every day for at least 2 days, followed by 500 mg ORALLY every day to complete a 7-10 day course of therapy ●**Disseminated infection due to Mycobacterium avium-intracellulare group** **-Prophylaxis**: 1,200 mg once weekly (may be combined with rifabutin); **-Advanced**: 600 mg ORALLY every day with ethambutol 15 mg/kg/day ●**Pharyngitis, Alternative for persons unable to take first line therapy**: 500 mg ORALLY on day 1, 250 mg/day on days 2-5	●**Acute exacerbation of chronic bronchitis**: (16 years & older) 500 mg ORALLY on day 1, 250 mg/day on days 2-5 ●**Acute otitis media**: (age 6 months and older) 30mg/kg as single dose or 10mg/kg every day x 3 days or 10 mg/kg on day 1 followed by 5 mg/kg every day for days 2-5 ●**Bacterial sinusitis, acute (Mild to Moderate)**: 10 mg/kg 1x/day for 3 days ●**Community acquired pneumonia (Mild to Moderate)**: (age 6 months and older) 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5 ●**Community acquired pneumonia (Mild to Moderate)**: (16 years & older) 500 mg on day 1, 250 mg/day on days 2-5 ●**Disseminated infection due to Mycobacterium avium-intracellulare group** **-Prophylaxis and Primary prevention**: 20 mg/kg once weekly (max 1200 mg/dose); **-Secondary prevention**: 5 mg/kg every day (max 250 mg) combined with ethambutol 15 mg/kg every day (max 900 mg/dose) (may be combined with rifabutin) **-Advanced:** once-daily doses of less than 5 mg/kg up to 20 mg/kg for 1 month or longer ●**Pharyngitis, Alternative for persons unable to take first line therapy**: (age 2 years and older) 12 mg/kg every day x 5 days; (16 years & older) 500 mg ORALLY on day 1, 250 mg/day on days 2-5

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of macrolides in treating adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, or *Mycobacterium avium* complex (MAC). Report authors drafted preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of the Washington State Preferred Drug Program (PDP). Prior to finalization, the key questions were posted for public comment on the Washington State Health Care Authority's Prescription Drug Program website (http://www.rx.wa.gov.) This process led to identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies.

Key Question 1: For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and *Mycobacterium avium* complex, do macrolide antibiotics differ in efficacy?

Key Question 2: For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis,

and *Mycobacterium avium* complex, do macrolide antibiotics differ in safety or adverse events?

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities, or in pregnancy for which one macrolide is more efficacious or associated with fewer adverse events?

Inclusion Criteria

Population(s):

Adult patients and children in outpatient settings with the following diagnosis:

- Community-acquired pneumonia
- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Otitis Media
- Streptococcal Pharyngitis
- *Mycobacterium avium* complex in HIV-infected patients

Interventions

- Erythromycin (ERYC®, Ery-tab®, Erythromycin Base Filmtab®, PCE Dispertab®, etc.)
- Clarithromycin (Biaxin®, Biaxin XL®)
- Azithromycin (Zithromax®, ZMAX®)

Effectiveness outcomes

- Clinical cure rate
- Bacteriological cure rate
- Percent switch to different antibiotic
- Hospitalization rates
- Mortality

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (nausea, vomiting, diarrhea, prolongation of QT interval, torsades de pointes, ventricular arrhythmias)

Study designs

- For efficacy, controlled clinical trials and good-quality systematic reviews
- For safety, controlled clinical trials, good-quality systematic reviews and observational studies.

The benefit of the randomized controlled trial (RCT) design is the ability to obtain a reliably unbiased estimate of treatment effects in a controlled setting. This is accomplished by using randomization to produce groups that are usually comparable based on both known and

unknown prognostic factors.[18, 19] However, RCTs can vary in quality, and often suffer from limitations in generalizability to the larger patient population. Observational study designs are thought to have greater risk of introducing bias, although they typically represent effects in a broader section of the overall patient population. While it has been shown that some observational studies and RCTs of the same treatments have similar findings, there are also multiple examples of situations where this has not been true and the question of what type of evidence is best has not been resolved.[20, 21] While RCTs also provide good evidence on short-term adverse events, observational designs are useful in identifying rare, serious adverse events which often require large numbers of patients exposed to a treatment over longer periods of time to be identified.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st quarter, 2006) Cochrane Database of Systematic Reviews (1st quarter, 2006) and Ovid® MEDLINE (1966 to September Week 3, 2005) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). We identified additional studies through searches of reference lists of included studies and reviews, the FDA web site, as well as searching dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

Each reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. In trials with crossover, outcomes for the first intervention were recorded if available. This was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a “carryover effect” (from the first treatment) in studies without a washout period, or “rebound” effect from withdrawal of the first intervention.

Data abstracted from observational studies included design, eligibility criteria duration, interventions, concomitant medication, assessment techniques, age, gender, ethnicity, number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up, number analyzed, and results.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.[22, 23] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix B), based on a clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive two different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Evidence Synthesis

An evidence report pays particular attention to the generalizability of efficacy studies performed in controlled or academic settings. Efficacy studies provide the best information about how a drug performs in a controlled setting because they allow for better control over potential confounding factors and bias. However, efficacy studies have some limitations, as the results are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria which may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have "comorbid" diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs, that are of value in actual practice. They often examine the short-term effects of drugs that, in practice, are used for much longer periods of time. Finally, they tend to use objective measures of effect that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Data Presentation

We constructed evidence tables detailing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated one macrolide against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptoms measured

using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Where possible, head-to-head data are the primary focus of the synthesis. No meta-analyses were conducted in this review due to heterogeneity in treatment regimens, use of concomitant medications, outcome reporting and patient populations.

In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

RESULTS

Overview

We identified 1,760 articles from literature searches and reviews of reference lists. This includes citations from dossiers submitted by pharmaceutical manufacturers. After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained copies of 429 full-text articles. After re-applying the criteria for inclusion, we ultimately included 110 publications. The flow of study inclusion and exclusion is detailed in Appendix C. It should be noted that while ideally studies that assessed all effectiveness outcomes were included, the majority of included studies did not report on two of these outcomes: percent switch to a different antibiotic and hospitalization rates.

Summary of main findings

- **Overview**
  - The limited number of direct comparisons between macrolides across all indications do not allow a definitive statement to be made that there is no difference among macrolides. However, very few differences among macrolides were demonstrated in the identified studies.
  - Based on limited head-to-head comparisons, erythromycin appears to have the highest incidence of adverse effects among macrolides. These adverse effects are primarily gastrointestinal in nature.

- **Efficacy**
  - **Direct comparative efficacy – head-to-head trials**
    - **Community Acquired Pneumonia – Adults**
      - Clinical cure rates were similar for all macrolides and ranged from 53-69% at the end of therapy. The majority of the remaining patients were classified as improved at that time point.
      - One study reported a higher clinical cure rate for clarithromycin in a questionable intent-to-treat analysis.
    - **Community Acquired Pneumonia - Children**
      - Clinical cure rates were similar and ranged from 76-100% in the studies.

- **Sinusitis - Adults**
  - Clinical cure rates ranged from 66 to 85% and bacteriological cure rates ranged from 86 to 93% across the three head-to-head trials identified for the treatment of acute bacterial sinusitis, suggesting no significant differences among any of the macrolides.
- **Sinusitis – Children**
  - Only two studies were identified examining macrolide use in children for the treatment of sinusitis. These studies were not included in the analysis as they were neither direct comparisons nor did they use the same active control.

- **Acute exacerbations of chronic bronchitis – Adults**
  - Clinical and microbiological response rates were similar for all macrolide comparisons (range 64-94% and 76-91% respectively.) A statistically significant difference in microbiologic response rate in favor of azithromycin was noted in one trial; however this result may have been influenced by the inclusion of patients infected by bacterial species against which the macrolides do not typically exhibit antibacterial activity. Furthermore, most AECB cases are of viral etiology, and the included trials varied in the rigor with which a bacterial etiology was established.
- **Acute exacerbations of chronic bronchitis – Children**
  - No appropriate trials of AECB/ABECB in children were identified in the literature search.

- **Otitis media - Adults**
  - The sole head-to-head trial in adults compared azithromycin to clarithromycin. No significant differences in either cure (azithromycin, 79%; clarithromycin, 74%) or improvement (azithromycin, 18%; clarithromycin, 23%) were noted.
- **Otitis media – Children**
  - In 2 fair-quality head-to-head trials of azithromycin and clarithromycin in children with AOM, no statistically significant differences in clinical response were noted. Clinical response rates in 1 trial were 100% for azithromycin and 95.7% for clarithromycin; in the second trial, response rates were 97% for azithromycin and 96% for clarithromycin
  - Microbiologic outcomes were not assessed in the 2 head-to-head trials in children with AOM.

- **Streptococcal Pharyngitis - Adults**
  - No differences in clinical cure were observed in fair quality direct comparisons of clarithromycin with either azithromycin (92% vs 92%) or erythromycin (80% vs 80%) in adults.
- **Streptococcal Pharyngitis – Children**

- No differences in clinical cure were observed in a fair quality direct comparison of azithromycin with clarithromycin (97 vs 96%). A single study fair quality study of azithromycin vs erythromycin (89 vs 65%, p=0.025 calculated) reported a higher clinical cure rate for azithromycin. No difference was observed when clinical response (cure/improvement) was reported (95 vs 98%).

- ***Mycobacterium avium* complex - Adults**
  - There were no direct comparison trials identified in the literature search examining the use of azithromycin or clarithromycin in the prophylaxis of MAC infection in HIV-infected patients.
  - Evidence of the comparative efficacy of azithromycin and clarithromycin was inconsistent across the only two head-to-head trials identified for the treatment of MAC infection. One study concluded there was no difference among the agents, where as the other study concluded clarithromycin to be significantly more efficacious than azithromycin. There were no clear factors identified to account for the discrepancy in sterilization rates, however, the difference in sample size may have contributed to the variation in results.
- ***Mycobacterium avium* complex – Children**
  - No clinical trials examining macrolide use in HIV-infected children either for treatment or prophylaxis of MAC infection were identified.

- **Indirect comparative efficacy – active and placebo-controlled trials**
  - Evidence from active-controlled trials comparing a macrolide to penicillin, amoxicillin, amoxicillin/clavulanic acid or dirithromycin found similar clinical and microbiological cure rates across all indications and comparisons.
  - One study found that when compared to placebo, azithromycin had a higher clinical cure rate (67.1% vs 79.3%) although this difference is not statistically significant. No studies compared placebo to clarithromycin or erythromycin.

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- **Safety**
  - **Direct comparative safety – head-to-head trials**
    - Erythromycin was associated with higher adverse event rates than clarithromycin in the majority of the available studies.
      - Overall adverse events were significantly higher for erythromycin in 3/5 studies, with no differences reported in the remaining 2 studies.
      - GI adverse events were significantly higher for erythromycin in 3/5 trials.

        - Significantly more patients withdrew from the erythromycin arm in 3/5 studies.
    - Erythromycin was associated with statistically higher overall adverse events than azithromycin in 3/6 trials.
        - The majority of AE's were GI in nature.
        - Discontinuation rates were low in all trials and not significantly different.
    - No significant differences in adverse event reports were identified between clarithromycin and azithromycin.
    - No significant differences were observed between the clarithromycin immediate release and extended release products.

- **Indirect comparative safety – active and placebo-controlled trials**
    - No conclusions about the relative safety and adverse event rates among the macrolides can be drawn from the active controlled trials.
    - Adverse events, particularly GI related, were higher for clarithromycin and azithromycin when compared to placebo in 3 total studies. No comparison among the macrolides can be made from this data.

- **Comparative efficacy and safety in subgroups**
    - No evidence is available to suggest that one macrolide is more efficacious or associated with fewer adverse events when used in any subgroup (including race, gender, concomitant medication use, and pregnancy) for any of the studied indications.

Detailed Assessment

Key Question 1. For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and *Mycobacterium avium* complex, do macrolide antibiotics differ in efficacy?

Community-acquired pneumonia.

Efficacy studies of macrolide monotherapy in non-hospitalized community-acquired pneumonia (CAP) patients were included in these reviews. The outcomes that were included in all studies were resolution of clinical signs and symptoms of infection and eradication of the organisms from the sputum if organisms were identified. Clinical cure was consistently defined as complete resolution of signs and symptoms of infection. Improvement was defined as incomplete resolution of signs and symptoms. Failure was a worsening or lack of improvement in clinical signs and symptoms. Hospitalization and mortality data were not reported in any of the trials.

Two trials comparing azithromycin to clarithromycin,[24, 25] four comparing azithromycin to erythromycin[26-29] and four comparing clarithromycin to erythromycin in adults or children were included.[30, 31] Only one of the studies was considered good quality[32], with the others rated fair for lack of blinding or failure to provide intention-to-treat analysis.[24-29, 33] No study

demonstrated a difference between agents in clinical cure. Data on microbiological cure are limited, with only two studies reporting results in a small number of isolates. The data are insufficient to draw firm conclusions regarding differences between macrolides in microbiologic cure.

Adults - Direct Comparisons

Azithromycin vs Clarithromycin. Two fair quality open-label studies of similar design comparing azithromycin and clarithromycin failed to show a difference in clinical outcomes or clinical cure rates.[24, 25] Both trials report enrollment of patients with mild to moderate pneumonia, but the definitions of severity are not included in either trial. Microbiological outcomes were assessed in only one of these trials[25], with similar eradication rates in excess of 90% for both treatment groups. *Haemophilus influenzae* and *Streptococcus pneumoniae* were the most frequently isolated bacterial species by culture.

Table 2. Azithromycin vs. clarithromycin in CAP patients

Trial (n)	Treatment	Duration	Clinical cure azi vs clari p value	Microbiological cure azi vs clari p value
Sopena, 2004[24] (n=63)	azithromycin 500mg po QD 3d vs clarithromycin 250mg BID	5 days azi 10 days amox	cure: 58.1 vs 68.8% improve: 38.7% vs 25% NS	NR
O'Doherty 1998[25] (n=176)	azithromycin 500mg po QD 3d vs clarithromycin 250mg BID	5 days azi 10 days amox	cure: 65% vs 69% improve: 30% vs 26% p=0.518	azi vs clari eradication 97% vs 91% NS all 7 serologic positive patients cured

See Appendix D for a listing of abbreviations used in the in-text tables.
For all tables, if p values were not reported they were calculated where possible.

Azithromycin vs. erythromycin. No difference in clinical response was observed in one trial including a small (n=41) number of patients with CAP from a larger respiratory infection study.[26] Microbiologic outcomes were not identified specifically for the CAP patients, but were not different for the entire study population.

Clarithromycin vs. erythromycin. One fair quality study reported higher clinical cure rates for clarithromycin.[30] Although no significant differences were observed between treatment groups in the per protocol population at the two-week post initiation of therapy visit (clinical success 98% clarithromycin vs 91% erythromycin, p=0.155), significant differences were observed at the same visit in the ITT population (success 89% clarithromycin vs 72% erythromycin, p=0.005). The major reason for exclusion of patients from the per protocol population (48% of the total enrolled) was a lack of confirmation of pneumonia prior to treatment, suggesting that nearly half of these patients may not have had pneumonia. No difference in clinical cure rates were observed in the remaining two fair quality studies of clarithromycin vs erythromycin in adults.[31, 32]

Severity of illness was explicitly reported in only one of the studies, with two-thirds patients having moderate infections and one-third having mild infections.[32] The other two studies enrolled patients who were considered "suitable" for oral therapy and reported no differences in severity of infection, but did not report the numbers of patients in any severity classification.[30, 31] The timing of evaluation was not explicitly defined in two of the studies.[31, 32] Chein, et al[32] reported two standard evaluation time periods, but reported only a single outcome measurement. Jang, et al[31] failed to report the timing of assessment completely.

Table 3. Clarithromycin vs. erythromycin in CAP patients

Trial (n)	Treatment	Duration	Clinical cure clari vs ery p value	Microbiological cure clari vs ery p value
Anderson G 1991[30] (n=108)	clari 250mg po BID vs ery stearate 500mg QID	14 days	cure: 45% vs 25%, p=.003 (90%CI 9.1-30.5) success: 89% vs 72%, p=.005 (CI 7.4-25.0)	eradication: 89% vs 100% NS only reported for evaluable patients
Jang, 1995[31] (n=40)	clari 250mg po BID vs ery (unspecified salt) 500mg QID	14 days	cure: 65% vs 65% NS improve: 95% vs 90% NS	NR
Chien, 1993[32] (n=173)	clari 250 q12 vs. erythro stearate 500 q6	7-14 days	cure: 62% vs 53% NS improve: 34% vs 43% NS	88% vs 100% p=.287

See Appendix D for a listing of abbreviations used in the in-text tables

Microbiological cure was reported in two of the studies,[30, 32] with no significant differences observed (rates 88-100%). The total number of pathogens from evaluable patients in both studies was small (n=14[30] and 43[32] respectively), reflecting the difficulty in culturing pathogens in the study population.

Children - Direct comparisons

Azithromycin vs clarithromycin. No head to head trials comparing azithromycin and clarithromycin in pediatric patients with CAP were identified.

Azithromycin vs erythromycin. No differences were observed in clinical efficacy in three fair quality studies comparing azithromycin and erythromycin.[27-29] The inclusion criteria of the studies was variable with respect to age and diagnoses. Two studies included three treatment arms, with azithromycin vs erythromycin arms for all patients 5-16 years and azithromycin vs. amox/clavulante for patients <5 years of age.[27, 29] Only data on the macrolide comparison arms are included in this analysis. A third study used a 3 treatment arm trial, with an unorthodox radiologic criteria of suspected atypical pneumonia necessary for inclusion in the macrolide comparison arm.[28] This inclusion criteria was significantly different from the age restrictions in the other trials. Clinical efficacy was variable but very high in all three studies (75.5-100%.)

Microbiological efficacy specific to the macrolide therapy portions of the studies was only reported in one of the studies and only for atypical pathogens.[27] No statistical differences were observed in eradication of the 35 identified pathogens.

Table 4. Azithromycin vs erythromycin in pediatric CAP patients

Trial (n)	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Azi	Ery	Azi	Ery
Harris, 1998[27] (n=420)	azi 10mg/kg *1d, then 5mg/kg days 2-5 vs erythromycin estolate 40mg/kg/d in 3 divided doses for 10 days (or amox/clav if <5 yrs; data not included)	5 days azi 10 days comparators	75.7% NS Improve: 21.7% NS	77.6% NS Improve: 20.9% NS	c.pneumonia eradication	
					75% NS	100 % NS
					mycoplasma eradication	
					100% p<0.05	67% p<0.05
Kogan, 2003[28] (n=59)	azi 10mg/kg *3d vs ery 50mg/kg/d in 3 divided doses for 14d (or amox 75mg/kg/d divided 3x/d for 7d not reported)	3 days azi 14 days ery	Symptom Free: 96.4% NS	Symptom Free: 92.3% NS	NR	
Wubbell, 1999[29] (N=147)	azi 10mg/kg *1d, then 5mg/kg days 2-5 vs erythromycin estolate 40mg/kg/d in 3 divided doses for 10 days (or amox/clav if <5 yrs; data not included)	5 days azi 10 days ery	100% NS	97% NS	NR	

See Appendix D for a listing of abbreviations used in the in-text tables

Clarithromycin vs erythromycin. No difference in clinical cure (84% clarithromycin vs 76% erythromycin) or microbiological efficacy (89% both groups) was reported in a fair quality study of clarithromycin vs erythromycin in children 3-12 years of age.[33] The majority of patients were 3-7 years of age with moderate severity of infection (defined as discomforting and disruptive to daily activites). Atypical pathogens *(Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) were the predominantly identified pathogens via culture or serology. Bacterial eradication rates were similar in both treatment groups.

Indirect Comparisons

Eight trials compared a macrolide to another non-macrolide antibiotic for treatment of CAP; no single non-macrolide antibiotic was compared to more than one macrolide.[34-35] No indirect comparisons of efficacy could be made as none of the active controls were compared to all of the available macrolides.

Acute bacterial sinusitis

Adults - Direct comparisons.

There were two head-to-head trials that examined response rates in patients with acute bacterial sinusitis.[36, 37] Both studies included patients with multiple conditions; however, the results were independently reported for sinusitis patients. A third trial compared immediate-release versus extended-release clarithromycin in patients with acute maxillary sinusits. No study reported a significant difference between macrolide antibiotics in clinical or bacteriologic cure.

Azithromycin versus Clarithromycin. No difference in clinical or bacteriologic cure rates were reported in a fair quality multiple condition study (i.e., patients presented with a variety of respiratory infections, including sinusitis) comparing azithromycin and clarithromycin.[37] Clinical cure was assessed on day 10-14 of therapy and was defined as the disappearance of clinical signs and symptoms observed prior to treatment. The rates reported were 66% for azithromycin and 68% for clarithromycin. Of the 67 patients with initial cultures, the bacterial eradication rate was 92% for azithromycin and 93% for clarithromycin.[37]

Azithromycin versus Erythromycin. Clinical and bacteriological cure rates were similar among azithromycin and erythromycin in a single fair quality head-to-head trial comparing these agents in patients with acute bacterial sinusitis. It included patients with multiple upper respiratory tract infections, the most predominant being sinusitis (65% of patients in the azithromycin group, and 67% of patients in the erythromycin group). Clinical efficacy was assessed at the latest examination period, 10-15 days after the start of therapy. Bacteriologic data were assessed in 124 patients. Of the 209 analyzed patients, the overall clinical cure rate was 83% for azithromycin and 79% for erythromycin (p=0.520). The clinical cure rate for the sinusitis group was 85% for azithromycin and 75% for erythromycin. Overall bacteriological eradication rate was 87% for azithromycin and 86% for erythromycin.[36]

Clarithromycin extended-release versus Clarithromycin immediate-release. There was one good quality, direct comparison of the extended-release and immediate-release formulations of clarithromycin. Patients with a diagnosis of acute maxillary sinusitis, confirmed by radiograph, received either clarithromycin ER 1000 mg once daily or clarithromycin IR 500 mg twice daily for fourteen days. The study did not include bacteriologic outcomes. Investigators found no significant difference in clinical cure between the two formulations in 245 assessable patients. The authors did note a statistically significant difference in compliance rates reported for the two formulations in both the ITT analysis and the evaluable patient analysis (ITT – 97% for ER, and 92% for IR, p=0.02).[38]

Table 5. Azithromycin, clarithryomycin and erythromycin in sinusitis patients

Trial	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
Muller 1993[37] (n=148)	azi 500 mg QD v clari 250 mg BID	3 days azi 10 days clari	azi: 66% NS	clari: 68% NS	azi: 92.1% NS	clari: 93.1% NS
Felstead 1991[36] (n=216)	azi 250 mg q12h day 1, 250 mg QD day 2-5 vs ery 250 mg QID	5 days azi 10 days ery	azi: 85% NS	ery: 75% NS	azi: 87% NS	ery: 86% NS
Murray 2000[38] (n=245)	clari ER 1000 mg QD vs clari IR 500 mg BID	14 days clari ER 14 days clari IR	clari ER: 85% NS	clari IR: 79% NS	clari ER: NS	clari IR: NR

See Appendix D for a listing of abbreviations used in the in-text tables

Indirect comparisons

Due to the lack of direct head-to-head evidence, a number of placebo-controlled and active-controlled trials were evaluated. In an effort to provide the best comparative data, only trials with similar active-controls were assessed. Thirteen placebo or active-controlled trials comparing a macrolide to amoxicillin, amoxicillin/clavulanic acid, phenoxymethylpenicillin, and placebo were included in the following tables; only eleven trials were included in analysis as two were rated poor quality.[36, 39-50] (Table 6)

Table 6. Summary of sinusitis placebo- and active-controlled trials

	Control			
Treatment	**Amox**	**Amox/Clav**	**Phenox**	**Placebo**
Azi	2 [36, 46]	3 [41-43]	1[40]	1[39]
Clari	3[47-49]	2 [44, 45]	0	0
Ery	0	0	1 [50]	0

See Appendix D for a listing of abbreviations used in the in-text tables

Azithromycin or Clarithromycin versus Amoxicillin/Clavulanic Acid. Azithromycin and clarithromycin were both associated with comparable clinical and bacteriologic cure rates relative to amoxicillin/clavulanic acid in 5 trials involving fairly similar patient populations.[41-45] (Table 7) One study utilized the extended-release formulation of clarithromycin.[45] Despite their similarities it is difficult to draw comparisons across the trials due to differences in study design, inclusion criteria, drug formulation, method and time of outcome assessment, and trial location. Overall, the clinical cure rates ranged from 71.5-98% for azithromycin and 64-93% for clarithromycin. It is important to note is that clinical cure rates for either agent did not differ significantly from the clinical cure for amoxicillin/clavulanic acid.

Table 7. Azithromycin and clarithromycin vs amoxicillin and clavulanic acid in sinusitis patients

Trial	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Macrolide	Amox/Clav	Macrolide	Amox/Clav
Henry 2003[41] (n=920)	azi 3 500 mg QD azi 6 500 mg QD a/c 500/125 mg TID	3 days azi 3 6 days azi 6 10 days a/c	azi 3: 71.5% (97.5% CI:8.4, 8.3) azi 6: 74.1% (97.5% CI:-5.6, 10.9)	71.5%	NR	NR
Clement 1998[42] (n=240)	azi 500 mg QD a/c 500/125 mg TID	3 days azi 10 days a/c	azi: 75% NS	70.3%	azi: 90.4% NS	83.9% NS
Klapan 1999[43] (n=97)	azi 500 mg QD a/c 500/125 mg q8h	3 days azi 10 days a/c	azi: 98% p>0.05	91% p>0.05	azi: 87% p=0.409	83% p=0.409
Dubois 1993[44] (n=260)	clari 500 mg q12h a/c 500/125 mg q8h	up to 14 days	clari: 64% NS	67%	clari: 87% p=0.56	90% p=0.56
Riffer 2005[45] (n=423)	clari ER 1000 mg QD a/c 875/125 mg TID	14 days	clari: 93% (95%CI:-4.2, 7.0)	92%	90% (95%CI:-10.2, 13.5)	89% (95%CI:-10.2, 13.5)

See Appendix D for a listing of abbreviations used in the in-text tables

Azithromycin or Clarithromycin versus Amoxicillin. Azithromycin and clarithromycin were both associated with similar levels of improvement relative to amoxicillin in four fair quality trials with similar patient populations that ranged in duration from 10 to 16 days.[36, 46-48] (Table 8) Clinical cure rates for a 5 day course of azithromycin were 73.9 and 84% versus a 10 day course of amoxicillin of 72 and 73%.Clarithromycin cure rates were 73-83% versus 71-85% for amoxicillin with durations of therapy ranging from 7 to 14 days. One of the clarithromycin trials was rated poor quality and is included in the tables but not the analysis.[49] The inclusion criteria were similar across trials with the exception of one azithromycin trial that included patients with a clinical diagnosis of sinusitis but not radiographic confirmation.[36] None of the studies included an intent-to-treat analysis. All three of the clarithromycin studies included the use of oxymetazoline nasal spray as part of the protocol, which may have an effect on rates of reported signs and symptoms and possibly clinical cure rates but would not alter bacteriologic cure rates.[47-49] Although the clinical cure rates appear quite similar for azithromycin and clarithromycin it is difficult to conclusively state comparative efficacy given the limited number of patients included and the differences described above. There was no statistically significant difference in any of the studies between azithromycin and amoxicillin or clarithromycin and amoxicillin.

Table 8. Comparative trials of amoxicillin in sinusitis patients

Trial	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Macrolide	Amoxicillin	Macrolide	Amoxicillin
Casiano 1991[46] (n=38)	azi 500 mg daily day 1, 250 mg daily day 2-5 amox 500 mg TID	5 days azi 10 days amox	azi 73.9% NS	73.3% NS	100%	100%
Felstead 1991[36] (n=244)	azi 500 mg daily day 1, 250 mg daily day 2-5 amox 500 mg TID	5 days azi 10 days amox	azi 81% p=0.599	72% p=0.599	azi 94% p=0.651	87% p=0.651
Calhoun 1993[47] (n=116)	clari 500 mg BID amox 500 mg TID	7-14 days	clari 73% (95%CI:-14.2, 18.7)	71% (95%CI:-14.2, 18.7)	NR	NR
Karma 1991[48] (n=68)	clari 500 mg Q12 hrs amox 500 mg Q8 hrs	9-11 days	clari 83% NS	85% NS	clari 89% (90%CI:-15.3, 9.3)	92% (90%CI:-15.3, 9.3)
Marchi 1990 [49] (n=114)	clari 500 mg BID amox 1000 mg BID	14 days	clari 78.9% NR	85% NR	clari 89%	93%

See Appendix D for a listing of abbreviations used in the in-text tables

Azithromycin versus Phenoxymethylpenicillin. One good quality study compared azithromycin to phenoxymethylpenicillin.[40] A dose of azithromycin 500 mg once daily for 3 days was compared with phenoxymethylpenicillin 1320 mg three times daily for 10 days. At visit 4 (23-27 days after the start of treatment) the clinical cure rate for azithromycin was 79.1% (n=220) and 75.5% (n=216) for phenyoxymethylpenicillin. There was no statistically significant difference in cure rates among the two agents at any time point evaluated.[40]

It is important to note that a large percentage of patients with rhinosinusitis have a viral infection or a self-limiting bacterial infection that will resolve without the use of antibiotics regardless of radiographic changes.[51, 52]

Children

There were two pediatric trials identified through the literature search. A full evaluation of these studies was not included as they were neither a direct comparison nor did they use the same active-control.[53, 54] Helin and colleagues reported results from a study comparing erythromycin, phenoxymethylpenicillin, and pivampicillin. The study included 92 children and improvement rates were reported as 80.0%, 83.5%, and 87.0% for erythromycin, phenoxymethylpenicillin, and pivampicillin respectively (no statistical analysis reported).[54] The second study by Ng et al. compared azithromycin to amoxicillin/clavulanic acid. Forty-one children were included in the analysis which reported 6 treatment failures in the azithromycin group and 5 failures in the amoxicillin/clavulanic acid group.[53]

Acute Exacerbations of Chronic Bronchitis, Acute Bacterial Exacerbations of Chronic Bronchitis

The study inclusion criteria and antibiotic interventions in the included acute exacerbations of chronic bronchitis (AECB) and acute bacterial exacerbations of chronic bronchitis (ABECB) trials may have an influence on the reported response rates and may explain some of the heterogeneity in responses observed among the various studies. The vast majority of AECB exacerbations in adults are of a viral, rather than bacterial, etiology. Ideally, AECB should be proven to be of a bacterial cause (i.e., ABECB) before antibiotics are administered, but this distinction is not always readily made in clinical practice. The rigor to which inclusion criteria in these trials allowed establishment of a bacterial etiology varied. Furthermore, there was some variation in the macrolide doses used in these trials. Finally, two of these trials included patients with a variety of conditions, rather than only patients with AECB/ABECB.

Adults - Direct comparisons

Azithromycin versus Clarithromycin. In 3 trials comparing azithromycin to clarithromycin (Table 9) there were no statistically significant differences in either clinical or microbiologic cure rates in two of these studies [55, 56] The third study found a statistically significant difference in favor of azithromycin in bacteriologic response only.[57]

Table 9. Azithromycin versus clarithromycin in AECB/ABECB patients

Trial	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Azi	Clari	Azi	Clari
Bradbury, 1993[55] (n=143)	azi 500 mg QD clari 250 mg BID	3 days azi 10 days clari	68% NS	64% NS	100% NS	93.1% NS
Pozzi, 1994[57] (n=205)	azi 500 mg QD clari 250 mg BID	3 days azi 7 days clari	94% NS	88% NS	93% p<0.05	75% p<0.05
Swanson, 2005[56] (n=318)	azi 500 mg QD clari 500 mg BID	3 days azi 10 days clari	85% NS	82% NS	85.7% NS	80.4% NS

See Appendix D for a listing of abbreviations used in the in-text tables

Azithromycin versus Erythromycin. The sole trial that compared azithromycin and erythromycin was a poor-quality trial of multiple conditions that included 138 patients with bronchitis, including patients with ABECB (the specific number of patients with ABECB was not reported).[26] Patients were randomized to receive either azithromycin (500 mg x 1, then 250 mg daily on days 2-5) or erythromycin stearate (500 mg four times daily for 7-10 days; a 7-day course was targeted, with the option to extend to 10 days if deemed appropriate). Clinical and bacteriologic responses were assessed at day 10-14 after the initiation of therapy. A positive clinical response was noted in 64% of azithromycin-treated patients and in 74% of erythromycin-treated patients. Microbiologic eradication was noted in 80% of patients given azithromycin and in 86% of erythromycin-treated patients, although these results encompass the entire study

population, and not only patients with ABECB. These differences in clinical response and microbiologic response were not found to be statistically significant.

Clarithromycin Extended-Release versus Clarithromycin Immediate-Release. Four studies were found that compared extended-release and immediate-release formulations of clarithromycin (Table 10).[58-61] While there were no statistically significant differences in clinical or microbiologic responses in any of these trials, doses and treatment durations varied across these studies.

Table 10. Clarithromycin extended-release vs immediate-release in AECB/ABECB patients

Trial	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			ER	IR	ER	IR
Adler, 2000[58] (n=182)	ER 1000 mg QD IR 500 mg BID	7 days	83% NS	82% NS	86% NS	85% NS
Gotfried, 2005[59] (n=444)	ER 1000 mg QD IR 500 mg BID	5 days ER 7 days IR	72% NS	76% NS	78% NS	82% NS
Nalepa, 2003[60] (n=703)	ER 500 mg QD IR 250 mg BID	5 days	90% NS	91% NS	79% NS	78% NS
Weiss, 2002[61] (n=162)	ER 500 mg QD IR 250 mg BID	7 days	81.8% NS	81.9% NS	71.4% NS	79.2% NS

See Appendix D for a listing of abbreviations used in the in-text tables

Indirect comparisons

The only active-controlled trials evaluated were those that included dirithromycin, a macrolide that is currently not available in the U.S.

Azithromycin, Clarithromycin, or Erythromycin versus Dirithromycin. Five trials compared dirithromycin with either azithromycin, clarithromycin, or erythromycin.[62-66] No statistically significant differences between azithromycin, clarithromycin, or erythromycin and treatment with dirithromycin were noted in any of these studies (Table 11). Note that 2 trials included significantly larger sample sizes than did the remaining trials.

Table 11. Dirithromycin comparative trials

Trial	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Macrolide	Diri	Macrolide	Diri
Castaldo, 2003[62] (n=83)	azi 500 mg/ 250 mg QD diri 500 mg QD	1-4 days azi 5 days diri	azi: 86.5% NS	93.2% NS	azi: NR	NR
Cazzola, 1999[63] (n=73)	azi 500 mg QD diri 500 mg QD	3 days azi 5 days diri	azi: 89.2% NS	94.4% NS	azi: 92.5% NS	90% NS

Table 11. Dirithromycin comparative trials (continued)

Trial	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Macrolide	Diri	Macrolide	Diri
Hosie, 1995[64] (n=212)	clari 250 mg BID diri 500 mg QD	7 days azi 5 days diri	clari: 95.5% NS	98.8% NS	clari: 71.9% NS	68.8% NS
Sides, 1993[65] (n=802)	ery 250 mg QID diri 500 mg QD	7 days ery 5 days diri	ery: 92.9% NS	88.5% NS	ery: 48.7% NS	57.4% NS
Wasilwes ki, 1999[66] (n=1057)	ery 250 mg QID diri 500 mg QD	7 days ery 5 days diri	ery: 71.5% NS	74% NS	ery: 45.2% NS	46.3% NS

See Appendix D for a listing of abbreviations used in the in-text tables

Children

No suitable trials of AECB/ABECB in children were identified. Chronic bronchitis (and, by extension, AECB/ABECB), is a disease that is almost exclusively confined to adult patients.

Otitis media.

Adults – Direct comparisons

Azithromycin versus Clarithromycin. A fair-quality head-to-head trial examined a total of 70 patients with AOM; this trial included patients with AOM, pharyngitis/tonsillitis, and sinusitis, and reported clinical responses for each individual condition.[37]. Patients were randomized to receive azithromycin 500 mg daily for 3 days or clarithromycin 250 mg twice daily for 10 days. Clinical responses were assessed at the end of therapy (day 10-14). A bacteriologic evaluation was also made on day 10-14, with eradication defined as organism eradication or a lack of culturable material. No significant differences in either cure, defined as the disappearance of clinical signs and symptoms (azithromycin, 79%; clarithromycin, 74%) or improvement, defined as an improvement in or partial disappearance of signs and symptoms, (azithromycin, 18%; clarithromycin, 23%) were noted.

Adults – Indirect comparisons

AOM is primarily a disease of children; few trials of AOM in adult patients were found in the literature search. As a result, a suitable number of trials including appropriate indirect comparisons was not found.

Children - Direct comparisons

Two fair-quality head-to-head trials of azithromycin versus clarithromycin examined clinical outcomes in pediatric patients with AOM.[67, 68] One study included 97 patients with clinical symptoms suggestive of uncomplicated AOM and otoscopic and tympanometric evidence indicative of AOM.[67] Patients were randomized to receive either azithromycin 10 mg/kg/day daily for 3 days or clarithromycin 15 mg/kg/day (divided in 2 doses per day) for 10 days. A satisfactory clinical response was defined as the complete resolution of initial clinical symptoms with or without the presence of middle ear fluid, while failure was defined as bacteriologic (inability to sterilize the middle ear fluid in patients with persistent ear drainage or who underwent repeated tympanocentesis) and/or clinical (the inability to clear initial clinical symptoms or the presence of persistent ear drainage by day 10-11). A systematic microbiologic assessment was not performed in this trial. Clinical success was found in 50/50 (100%) of azithromycin-treated patients and in 45/47 (95.7%) of clarithromycin-treated patients.[67] In the second study, 133 patients with clinical symptoms and otoscopic and tympanometric evidence suggestive of AOM received either azithromycin (10 mg/kg on day 1 followed by 5 mg/kg on days 2-5) or clarithromycin 7.5 mg/kg/day twice daily for 5 days.[68] A satisfactory clinical response was defined as clinical cure, cure with effusion, or improvement. A bacteriologic evaluation was not performed. Clinical success at day 25 was reported in 97% of azithromycin-treated subjects and in 96% of clarithromycin-treated patients. Neither of these studies found a statistically significant difference in response between azithromycin and clarithromycin.

Children - Indirect comparisons

While a number of active-controlled trials of macrolides in AOM were identified, the only active control to which all macrolides were compared was amoxicillin, which remains the standard of care for AOM.

Azithromycin, Clarithromycin or Erythromycin versus Amoxicillin. Five trials comparatively evaluated a macrolide and amoxicillin (Table 12) [69-73]. Only one of the five studies evaluated found a statistically significant difference in clinical response rates between the macrolide and amoxicillin (this trial compared azithromycin and amoxicillin)[70] It is difficult to identify any particular reason that only this trial found a statistically significant difference in favor of the macrolide, although azithromycin-resistant pathogens were identified in 5 patients assigned to receive azithromycin (all of these patients were classified as clinical cures), while 17 amoxicillin-treated patients were infected with amoxicillin-resistant pathogens (2 of these patients were considered clinical failures). Of the four remaining trials, the macrolide treatment arm was associated with a trend toward a superior clinical response in two trials[69, 72] (azithromycin and clarithromycin), inferior response in one[71] (clarithromycin), and no significant difference in one trial[73] (erythromycin). It is difficult to make meaningful comparisons between macrolides in these active-control trials due to the limited number of studies as well as the variability in patient demographics (age, presence or absence of bacteriologic confirmation of AOM), clinical response rates, timing and method of outcome assessment, and the duration and dosage of each treatment (doses of the 3 macrolides varied among the various trials).

When evaluating patients for inclusion in these trials, four trials utilized otoscopic or tympanometric examination to verify the diagnosis of AOM,[69, 71-73] while one trial utilized

clinical symptoms only in the diagnosis of AOM; according to current guidelines, otoscopic confirmation is required to establish the diagnosis of AOM in clinical trials.[70] One trial included a systematic assessment of microbiologic responses,[69] but these data were not reported; one trial was designed to perform this analysis, but the number of patients who were found to exhibit a pathogen in the middle ear fluid upon enrollment was not sufficient to allow statistical analysis of microbiologic responses. According to current treatment guidelines, an appropriate trial of antimicrobial therapy for AOM should include a pre-therapy confirmation of a bacterial etiology (many cases of AOM are of a viral etiology) and a post-therapy assessment of bacteriologic response in the middle ear fluid (a so-called "double tympanocentesis study"). [70]

Table 12. Macrolides vs amoxicillin in otitis media patients

Trial	Treatment and duration		Clinical cure p value	
	Macrolide	Amoxicillin	Macrolide	Amoxicillin
Arguedas, 2005[69] (n=312)	azi 30 mg/kg QD, 1 day	45 mg/kg BID, 10 days	azi 77% NS	74% NS
Mohs, 1993[70] (n=154	azi 10 mg/kg QD, 3 days	10 mg/kg TID, 10 days	azi 83% p=0.003	60% p=0.003
Pukander, 1993[71] (n=47)	clari 7.5 mg/kg BID, 7-10 days	20 mg/kg BID, 7-10 days	clari 37% NS	55% NS
Coles, 1993[72] (n=219)	clari 125 mg BID (wt ≤ 25 kg) or 250 mg BID (wt > 25 kg), ~ 5 days	125 mg TID (wt < 25 kg) or 250 mg TID (wt ≥ 25 kg),~ 5 days	clari 77% NS	68% NS
Scholz, 1998[73] (n=280)	ery 20 mg/kg BID, 10 days	25 mg/kg BID, 10 days	ery 93.6% NS	95.7% NS

Bacteriological cure rates were not reported for these studies
See Appendix D for a listing of abbreviations used in the in-text tables

Pharyngitis

Clinical cure was universally defined as complete resolution of clinical signs and symptoms across all studies. Improvement was defined as incomplete resolution of signs and symptoms.

Adults – Direct Comparisons

Azithromycin versus clarithromycin. No efficacy differences in clinical cure were observed between azithromycin and clarithromycin in either head to head efficacy study of azithromycin vs clarithromycin.[37, 74] Muller, et al included pharyngitis as part of a larger indication pool, but reported response rates for this indication.

The microbiological results were disparate between the studies, though the absolute differences in rates were minor. Muller, et al, report high, identical eradication rates (95%) in both groups.[37] In Kaplan, et al, azithromycin was more effective than clarithromycin at eradicating *S. pyogenes* at both early (95 vs 88%, p=0.019) and late follow-up visits (91 vs 82%,

p=0.012).[74] No differences in age (mean 26 years), gender, ethnicity, or baseline symptoms were observed between the groups. Compliance rates were 92% and 98% for clarithromycin and azithromycin, respectively. A definitive conclusion on microbiological differences of effect can not be made.

Table 13. Azithromycin vs clarithromycin in pharyngitis patients

Trial (n)	Treatment	Clinical cure p value		Microbiological cure p value	
		Azi	Clari	Azi	Clari
Kaplan 2001[74] (N=392)	clari 250mg BID vs azi 500mg day 1, 250mg po QD days 2-5	92% NS	92% NS	95% p=0.019	88% p=0.019
Muller 1993[37] (n=144, pharyngitis only)	azi 500mg QD vs. clari 250mg BID	76% improved: 20% NS	74% improved: 23% NS	95% (pharyngitis and tonsillitis pts combined) NS	95% (pharyngitis and tonsillitis pts combined) NS

See Appendix D for a listing of abbreviations used in the in-text tables

Clarithromycin vs erythromycin. No difference in clinical (80% each group) or microbiological efficacy (91% azithromycin vs 98% clarithromycin, p=NS) was observed in this study.[75] The mean age of the patients was higher in this study (44 years of age) than in other reviewed pharyngitis studies. No differences in efficacy were observed when comparing treatment in patients greater than 64 years of age.

Children – Direct comparisons

Azithromycin vs clarithromycin. No differences in clinical or microbiological efficacy were observed in the only study of pediatric patients receiving azithromycin vs clarithromycin.[76] Clinical cure rates were very high (96-97%) in both groups, even though the only evaluation time point of 10 days was earlier than most other studies. Microbiological efficacy was similarly high (95%) in both groups. A modified ITT analysis including the children who did not complete treatment (19 clari, 5 azi) was reported for bacterial efficacy. In the mITT, azithromycin was significantly better at eradicating *S. pyogenes* (93.6% vs 82.9%, p<0.05).

Azithromycin vs erythromycin. No differences were observed for clinical or bacterial efficacy in a single open-label study comparing azithromycin vs erythromycin.[77] More patients were assigned a designation of "cured" in the azithromycin arm (86% vs 65%, p=NR). However, this difference was eliminated when clinical success (cure or improved) was reported (96% vs 98%). Bacterial eradication was reported in 91% and 98% of patients treated with azithromycin and erythromycin, respectively.

Clarithromycin vs erythromycin. No efficacy studies are available comparing clarithromycin vs erythromycin in pediatric patients with streptococcal pharyngitis.

Adults - Indirect comparisons

Among the numerous active-controlled trials of macrolides, the only active control to which all macrolides were compared was penicillin. For this reason, and because penicillin is considered first-line therapy for streptococcal pharyngitis, only these trials were evaluated. One azithromycin vs penicillin,[78] four clarithromycin vs penicillin,[79-82] and two clarithromycin ER vs penicillin[83, 84] studies were identified. No differences in clinical efficacy for macrolides versus penicillin therapy were identified in any of the studies. No differences in microbiological eradication were identified in seven of the eight penicillin controlled studies. One study reported a higher eradication rate for clarithromycin at the early follow-up visit.[80] This difference lost statistical significance when compared at the late follow-up visit. One possiblility for this single study discrepancy was the low dose of penicillin utilized. Overall differences in penicillin clinical (77-98%) and microbiological (83 -97%) response rates preclude their usage for meaningful comparisons across macrolides.

Table 14. Azithromycin and clarithromycin vs penicillin pharyngitis patients

Trial (n)	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Macrolide	Pen	Macrolide	Pen
Hooten 1991[78] (n=254)	azi 500mg day 1, 250 day 2-5 vs pen 250mg QID	5 days azi 10 days pen	azi: 86.8% NS	77.8% NS	azi: 90.8% NS	95.6% NS
Bachand, 1991[79] (n=90)	clari 250 q12 vs pen VK 250 q6h	NR	clari: 86% NS	77% NS	clari: 88% NS	91% NS
Schrock 1992[80] (n=356)	clari 250 q12 vs pen VK 250 q8h	10 days	clari: 89% NS (4-6d post tx)	85% NS (4-6d post tx)	clari: 95% p=0.009 (4-6d post cure)	87% p=0.009 (4-6d post cure)
Stein 1991[81] (n=97)	clari 250 q12 vs pen VK 250 q6h	10 days	clari: 79% NS	79% NS	clari: (eradication) 87% NS	(eradication) 85% NS
Levenstein 1991[82] (n=125)	clari 250mg q12 vs pen 250mg q6h	8-10 days clari 10-14 days pen	clari: 96% NS (2-10d post tx)	98% NS (2-10d post tx)	clari: 100% NS (2-10d post tx)	97% NS (2-10d post tx)
Takker 2003[83](n=362)	clari 500mg ER QD vs pen 500mg TID	5 days clari 10 days pen	clari: 92% p=0.274	89% p=0.274	clari: 82% p=0.598	83% p=0.598
Portier 2002[84] (n=239)	clari MR 500mg QD vs 590mg (1MU) pen TID	5 days clari 10 days pen	clari: 88.1% NS (3d post tx)	92.4% NS (3d post tx)	clari: 82.8% NS (3d post)	83.6% NS (3d post)

See Appendix D for a listing of abbreviations used in the in-text tables

Children – Indirect comparisons

One erythromycin, six azithromycin, and two clarithromycin vs penicillin studies were identified; one study reported a difference in clinical efficacy.[85] In the sole study reporting a statistical difference in clinical cure (erythromycin 87% vs penicillin 98%), the erythromycin duration was 5 days, much shorter than the usual 10 day duration.[85] The 87% clinical cure rate for erythromycin was similar to the cure rates with other macrolides. The two clarithromycin studies used identical drug doses and had comparable patient populations, but different durations of macrolide therapy and reported very different clinical response rates for the penicillin arms, though similar clarithromycin cure rates.[86, 87] The lack of a consistent effect, as demonstrated by penicillin cure rates of 78-95%, makes further comparisons suspect. No conclusions can be drawn on potential differences in macrolide clinical or microbiological efficacy from penicillin controlled trials.

Table 15. Macrolides vs pencillin pediatric pharyngitis patients

Trial (n)	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Macrolide	Pen	Macrolide	Pen
Adam 1996[85] (n=201)	ery estolate 40mg/kg/d BID vs pen V 30mg/kg/d TID	5 days ery 10 days pen	ery: 87.2% p<0.01 success (cure or improved): 98%	98.0% p<0.01 success (cure or improved): 98%	ery: 83.3% NS	87.9% NS
Cohen,2002[88] (n=469)	azi 10mg/kg qd vs azi 20mg/kg vs 45mg/kg/d pen vk in 3 divided doses	3 days azi 10 days pen	azi 10: 83.4% azi 20: 91.5% p=0.024 (day 14 ITT group)	92.8% p=0.024 (day 14 ITT group)	azi 10: 50% azi 20: 86% p=0.0001 (day 14 ITT group)	82.5% p=0.0001 (day 14 ITT group)
Hamill, 1993[89] (n=85)	azi 10mg/kg qd vs 125 (<20kg)-250mg pen vk QID	3 days azi 10 days pen	azi: 93% NS (day 9-11)	93% NS (day 9-11)	azi: 95% NS (day 9-11)	95% NS (day 9-11)
O'Doherty 1996[90] (n=358)	azi 10mg/kg qd vs azi 20mg/kg vs 125 (<20kg)-250mg pen vk QID	3 days azi 10 3 days azi 20 10 days pen	azi 10: 99% azi 20: 100% NS (day 12-14)	97% NS (day 12-14)	azi 10: 98% azi 20: 98% p=0.011 (day 12-14)	92% p=0.011 (day 12-14)
Pacifico 1996[91] (n=154)	azi 10mg/kg qd vs pen 50,000IU/d in 2 divided doses	3 days azi 10 days pen	azi: 85.5% NS (day 12-14)	93.6% NS (day 12-14)	azi: 67.1% p≤0.025 (day 12-14)	91.0% p≤0.025 (day 12-14)
Schaad 1996[92] (n=320)	azi 10mg/kg qd vs pen 56 (100,000IU) mg/kg/d in 3 divided doses	3 days azi 10 days pen	azi: 83% NS (day 10-12)	82% NS (day 10-12)	azi: 65% p<0.001 (day 10-12)	82% p<0.001 (day 10-12)

Table 15. Macrolides vs pencillin pediatric pharyngitis patients (continued)

Trial (n)	Treatment	Duration	Clinical cure p value		Microbiological cure p value	
			Macrolide	Pen	Macrolide	Pen
Schaad 2002[93] (n=269)	azi 10mg/kg qd vs 56 (100,000IU) mg/kg/d in 3 divided doses	3 days azi 10 days pen	azi: 77% NS (day 14)	85% NS (day 14)	azi: 38% p<0.001 (day 14)	81% p<0.001 (day 14)
McCarty 2000[86] (n=497)	clari 7.5mg/kg twice daily for vs 13.3mg/kg pen TID	5 days clari 10 days pen	clari: 97% NS (48h post-tx)	94% NS (48h post-tx)	clari: 94% p<0.001 (post-tx visit - 2d post)	78% p<0.001 (post-tx visit - 2d post)
Still 1993[87] (n=367)	clari 7.5mg/kg twice daily vs 13.3mg/kg pen TID for	10 days clari 10 days pen	clari: 86% NS	80% NS	clari: 92% p=0.004	81% p=0.004

See Appendix D for a listing of abbreviations used in the in-text tables

Mycobacterium avium complex

Mycobacterium avium complex (MAC) consists of *Mycobacterium avium*, *Mycobacterium intracellulare*, and other atypical mycobacteria in less-significant quantities. MAC is an opportunistic infection usually associated with immunocompromise and can often be seen in human immunodeficiency virus (HIV) infected patients. Since HIV-infected patients are the largest single population of patients affected by MAC infection, only trials examining treatment and prophylaxis among HIV-infected patients were included in analysis.

Adults - Direct Comparisons

MAC infection in patients infected with HIV is always treated with a multi-drug regimen. Most often one of the medications included in the regimen is a macrolide antibiotic, either azithromycin or clarithromycin (erythromycin has much lower in vitro activity against mycobacteria). The clinical trials examining treatment of MAC are largely designed to evaluate the efficacy of multi-drug regimens. Of 18 trials examining the treatment of MAC identified through the literature search; only 3 allowed any direct comparison of azithromycin and clarithromycin[94-96]. One of these was of poor quality[96] and was not included in the comparative analysis.

Azithromycin versus Clarithromycin. Two studies allowed direct comparisons of the efficacy of azithromycin and clarithromycin in the treatment of MAC.[94, 95] The primary outcome measure for both studies was sterilization of the blood. One trial reported a statistically significant difference among sterilization rates at week 16, reporting a rate of 94.4% for clarithromycin and a rate of 45.5% for azithromycin (p=0.011),[95] while the second study reported sterilization rates at week 24 as 56% for clarithromycin and 46% for azithromycin

(p=0.24).[94] The difference in outcome could be due partially to a difference in the study population; it is possible the larger number of patients in the study by Dunne and colleagues would allow for better distribution of baseline characteristics such as other underlying opportunistic infections or severity of illness. However, neither study met their initial enrollment goal, decreasing their overall predictive ability. One of the studies included mortality as a secondary outcome.[94] There was no significant difference reported in death rates for azithromycin and clarithromycin. Despite the fact that dosing considerations are outside the scope of this review it is important to note that studies have reported greater toxicity and mortality with clarithromycin doses greater than 500 mg twice daily.[97] The clinical efficacy of clarithromycin is well-established, while the comparative efficacy of azithromycin remains less well-defined. Although somewhat limited, the evidence examined appears to favor clarithromycin for treatment of MAC.

Table 16. Azithromycin vs clarithromycin in MAC patients

Trial	Treatment	Additional treatment	Blood sterilization rates at latest follow-up	Hazard ratio p value	Deaths
Dunne, 2000[94] (n=125)	azi 250 mg QD azi 600 mg QD clari 500 mg BID	Ethambutol 800 mg or 1200 mg based on patient weight	azi 250 NR azi 600 53% clari 60%	0.8 (95% CI 0.5-1.2) p=0.24	azi 250 25* azi 600 47 clari 36
Ward, 1998[95] (n=59)	azi 600 mg QD clari 500 mg BID	Ethambutol 800 mg or 1200 mg based on patient weight	azi 45.5% clari 94.4% (at week 16)	NR p=0.011	8 total deaths

**Deaths for azi 250 group reported only at interim analysis, includes all-cause mortality reported for 40 patients*

Indirect comparisons

There were no trials identified that allowed for indirect comparisons of azithromycin and clarithromycin in the treatment of MAC infection in HIV-infected patients.

Prophylaxis - Direct comparisons

There were no direct comparison trials identified in the literature search examining the use of azithromycin or clarithromycin in the prophylaxis of MAC infection in HIV-infected patients.

Prophylaxis - Indirect comparisons

Due to the lack of direct head-to-head evidence, available placebo-controlled and active-controlled trials were evaluated. Two placebo-controlled trials were examined, one each comparing azithromycin and clarithromycin to placebo, and two active-control trials were also included each comparing azithromycin or clarithromycin to rifabutin and itself plus rifabutin. [98-101]

Azithromycin or Clarithromycin versus Placebo. Azithromycin and clarithromycin were both significantly better at preventing MAC infection than placebo in the two good-quality trials evaluated. Although the primary endpoint of the clarithromycin study was time to MAC infection, the reported infection rates were 6% for the clarithromycin group and 16% for the placebo group (p<0.001, hazard ratio 0.31).[101] The intent-to-treat analysis for the azithromycin trial, reported the development of MAC infection 30 days after the last dose as 10.6% of azithromycin patients and 24.7% of placebo patients (p=0.004, hazard ratio 0.34).[100] Pierce and colleagues also examined mortality as a secondary endpoint, reporting significantly more deaths in the placebo arm (p=0.026, HR 0.75, 95%CI 0.58-0.97). Both trials were terminated early due to concerns over the use of placebo in these patients. The rates of infection cannot be compared directly across the studies due to differences in design, primary endpoints, and timing of outcome assessment.

Azithromycin or Clarithromycin versus Active-control. There were two active-control trials evaluated for comparative purposes.[98, 99] Both trials had three treatment arms: azithromycin or clarithromycin alone, rifabutin alone, and azithromycin or clarithromycin plus rifabutin. The results of both studies suggest the macrolide agent alone and in combination with rifabutin were superior to rifabutin alone for prophylaxis. The intent-to-treat analysis of the clarithromycin study revealed confirmed MAC infection in 9% of clarithromycin patients, 7% of clarithromycin plus rifabutin patients, and 15% of rifabutin alone patients.[98] The other study reported similar incidence rates: 13.9% for azithromycin group, 8.3% for azithromycin plus rifabutin group, and 23.3% for the group on rifabutin.[99] Once again there was a major difference in the primary endpoints set by the two studies. The azithromycin study examined time to the development of MAC infection while the clarithromycin study was designed to look at incidence of MAC infection. Mortality was listed as a secondary outcome measure in both trials. Although the outcomes were reported differently, there was no significant difference found in either study. Based on the limited available evidence, both azithromycin and clarithromycin appear more effective than placebo and rifabutin in the prophylaxis of MAC infection.

Table 17. Placebo-control and active-control trials for MAC prophylaxis

Trial	Treatment	Incidence of MAC infection at last follow-up	Hazard ratio p value	Deaths†
Pierce, 1996[101] (n=667)	clari 500 mg BID placebo	clari 6% placebo 16%	0.31 p<0.001	clari 107 placebo 137
Oldfield, 1998[100] (n=174)	azi 1200 mg QW placebo	azi 15.3% placebo 30.3%	0.41 p=0.006	azi 38 placebo 38
Havlir, 1996[99] (n=664)	azi 1200 mg QW rifa 300 mg QD azi 1200 mg QW + rifa 300 mg QD	azi 13.9% rifa 23.3% azi+rifa 8.3%	azi vs rifa 0.53 p=0.008	azi 83 rifa 85 azi+rifa 81
Benson, 2000[102] (n=1178)	clari 500 mg BID rifa 450/300* mg QD clari 500 mg BID + rifa 450/300 mg QD	clari 9% rifa 15% clari + rifa 7%	clari vs rifa 0.56 p=0.005 (reported as risk ratio)	clari 167 rifa 168 clari + rifa 179

**9 months into the study the dose of rifabutin was decreased from 450 mg QD to 300 mg QD due to the incidence of uveitis; † Mortality evaluated as secondary outcome in all trials except Oldfield 1998; See Appendix D for a listing of abbreviations used in the in-text tables*

Children

No clinical trials examining macrolide use in HIV-infected children either for treatment or prophylaxis of MAC infection were identified.

Key Question 2: For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and *Mycobacterium Avium* complex, do macrolide antibiotics differ in safety or adverse events?

The evidence is limited and insufficient to compare all three macrolides with respect to adverse events. The absolute rates of adverse events vary several-fold among studies of the same drugs. Further, considerable variability was observed in the reporting and classification of these side effects. It is important to note that these efficacy trials were not designed to detect differences in adverse events

The most frequently reported AEs are gastrointestinal (nausea, vomiting, diarrhea and abdominal pain). A serious event reported with macrolide therapy is prolongation of the QT interval resulting in Torsades de Pointes. No reports of Torsades de Pointes or any other arrhythmias were reported in any of the efficacy studies included in this review. A review of the FDA voluntary reporting system MedWatch was published in 2002. Although the relative ability of the macrolides to cause arrhythmias is difficult to ascertain, clarithromycin was reported more frequently than erythromycin.[103] Azithromycin was very infrequently identified as a potential cause. These data should be interpreted cautiously as other predisposing factors for Torsades were identified, as was coadministration of other drugs known to alter heart electrophysiology.

The only significant difference reported in adverse events was found in three trials suggesting erythromycin adverse events were more frequent than those with clarithromycin.[30-32]

Placebo-controlled studies

Three placebo-controlled trials reported adverse events.[39, 100, 101] Comparison of adverse effects is limited by the number of studies, the populations studied (two HIV trials) and the differences in the dosage regimens used. Rate of withdrawal due to adverse events was greater for daily clarithromycin compared to weekly azithromycin in MAC prophylaxis, but neither drug was significantly different from its placebo control.

Table 18. Adverse events in placebo-controlled studies

Trial (n) Indication	Treatment	Duration (days)	Mean age % male	All adverse events		Gastrointestinal adverse events		Withdrawals	
				Macrolide	Placebo	Macrolide	Placebo	Macrolide	Placebo
Haye 1998[39] (169) Sinusitis	azi 500 mg qd placebo qd	3 days	azi 40.2 placebo 43.2 26.0% M	azi 27.6% p=0.15	18.3% p=0.15	azi 24.1% p<0.01	8.5% p<0.01	0% NR	0% NR

Table 18. Adverse events in placebo-controlled studies (continued)

Trial (n) Indication	Treatment	Duration (days)	Mean age % male	All adverse events		Gastrointestinal adverse events		Withdrawals	
				Macrolide	Placebo	Macrolide	Placebo	Macrolide	Placebo
Oldfield 1998[100] (182) MAC prophylaxis	azi 1200 mg qw placebo qw	30-985*** 36-1018***	azi 41.1 placebo 38.2 92.8% M	NR	NR	azi 78.9% p<0.001	27.5% p<0.001	8.2% azi p=0.14	2.3% p=0.14
Pierce 1996[101] (682) MAC prophylaxis	clari 500 mg bid placebo bid	NA	clari 37.5 placebo 37.6 91.1% M	42% clari*† p<0.001	26%*† p<0.001	clari 28% p=0.004	18% p=0.004	clari 8%*† p=0.45	6%*† p=0.45

*Includes adverse effects that were possibly, probably, or definitely related to the administration of the study drug and unrelated to any concurrent condition
** Percentages based of the reported percentages in All AE column
*** Patients were to remain in study for at least 18 months; they could receive study drug until documented MAC infection or death unless withdrawn for other reasons
†Analysis included all patients who received study medication, it was unclear what number of patients received medication as only percentages were reported

Direct Comparisons

Clarithromycin vs Erythromycin

Inconsistent data are available from head-to-head studies that compare the adverse event profiles of clarithromycin and erythromycin. The only significant differences reported suggest erythromycin may be more poorly tolerated.

Five trials of clarithromycin vs erythromycin reported adverse event rates. Erythromycin had a significantly greater incidence of overall side effects in two of the trials,[30, 32] while a third reported no difference.[33] Specific GI side effects were significantly higher in the erythromycin treated subjects in three of the four studies that reported these data[30-32]; there was a trend toward higher incidence with erythromycin in a fourth.[75] The dosing of both agents was similar among studies.

Table 19. Adverse Events – clarithromycin vs erythromycin

Trial (N) Indication	Treatment	Mean age (yr) % male		All adverse events		GI adverse events		Withdrawals	
		Clari	Ery	Clari	Ery	Clari	Ery	Clary	Ery
Chien, 1993[32] (268) CAP	clari 250 q12 * 7-14d vs. erythro stearate 500 q6 * 7-14d	47.2 51% M	48.2 51% M	30.8% p<0.001	58.5% p<0.001	18.8% p<0.001	51.8% p<0.001	4.5% p<0.001	27.4% p<0.001

Table 19. Adverse Events – clarithromycin vs erythromycin (continued)

Trial (N) Indication	Treatment	Mean age (yr) % male		All adverse events		GI adverse events		Withdrawals	
		Clari	Ery	Clari	Ery	Clari	Ery	Clary	Ery
Block, 1995[33] (260) CAP	clari 15mg/kg/d divided q12 * 10d vs EES 40/mg/kg/d divided BID or TID * 10d	NR (age range 3-12) 61% M p=0.0	(age range 3-12) 46% M p=0.0	24% NS	23% NS	NR	NR	3 pts NR	5 pts NR
Anderson G 1991[30] (208) CAP	clari 250mg po BID vs erythromycin stearate 500mg QID for 14 days	53.5 56% M	53.5 56% M	19% p=0.012 due to drug: 16% p=0.004	35% p=0.012 due to drug: 33% p=0.004	7% p=0.001	27% p=0.001	4.1% p<0.01	18.8% p<0.01
Jang, 1995[31] (40) CAP	clari 250mg po BID vs erythromycin (not specified salt) 500mg QID for 14 days	clari 53.6 36% M	ery 54.3 36% M	clari 5% p<0.05	ery 30% p<0.05	5% p<0.05	30% p<0.05	0% NS	10% NS
Scaglione 1990[75] (240) Pharyngitis	clari 250mg bid vs ery stearate 500mg bid for 10 days	clari 43.97 62% M	ery 43.97 62% M	clari 5.8% NR	ery 10% NR	5.8% NR	10% NR	0.8% p<0.025	6.7% p<0.025

Azithromycin vs Erythromycin

Three[26-28] of the six [26-29, 36, 77] available head-to-head trials described a significant increase in adverse events for erythromycin when compared to azithromycin. Gastrointestinal side effects were predominantly reported. No differences in patient withdrawal from the study were noted by treatment group.

Table 20. Adverse events – azithromycin vs erythromycin

Trial (n) Indication	Treatment		Duration (days)		Mean age % male		All AE		GI AE		Withdrawals	
	Azi	Ery	Azi	Ery	Azi	Ery	Azi	Ery	Azi	Ery	Azi	Ery
Felstead 1991[36] (216) Sinusitis	250 mg q12h day 1, 250 mg qd day 2-5	250 mg qid	5 days	10 days	40.8 61%	39.6 61%	18% NR	19% NR	diarrhea and/or nausea: 14.3%	diarrhea and/or nausea: 14.4%	1% azi NR	1.8% NR

Table 20. Adverse events – azithromycin vs erythromycin (continued)

Trial (n) Indication	Treatment		Duration (days)		Mean age % male		All AE		GI AE		Withdrawals	
	Azi	Ery	Azi	Ery	Azi	Ery	Azi	Ery	Azi	Ery	Azi	Ery
Daniel, 1991[26] (181) AECB/ABECB, CAP	500 mg x 1, 250 mg QD	500 mg QID	5 days	7-10 days	57.7 51.4 %	58.8 51.4 %	5% p<0.01	18% ery p<0.01	NR	NR	0% NR	1% NR
Harris, 1998[27] (456, 3 arms) CAP	10mg/kg *1d, then 5mg/kg days 2-5	40mg/kg/d in 3 divided doses	5 days	10 days	5.53 53.7 %	5.22 61.5 %	10.4% p <0.05	20.0% p <0.05	diarrhea: 6.1% vomiting: 9.2% abd pain: 7.4% nausea: 5.5%	diarrhea: 22.7% vomitting: 39.3% abd pain: 20.0% nausea: 10.7%	1.8% NR	1.3% NR
Kogan, 2003[28] (59, 3 arms) CAP	10mg/kg	50mg/kg/d in 3 divided doses	3 days	14 days	5.23 NR	4.68 NR	0% p <0.05	11.5% p<0.05	diarrhea: 0% azi p<0.05	diarrhea: 11.5% p<0.05	0 for both interventions	
Wubbell, 1999[29] (174, 3 arms) CAP	10mg/kg *1d, then 5mg/kg days 2-5	40mg/kg/d in 3 divided doses	5 days	10 days	47% 0-2 16% 3-4 25% 5 to 8 12% 9-16 only >5 included in analysis here		14% NR	25% NR	diarrhea: 4.3% vomiting: 1.4% abd pain: 2.9% nausea: 0% azi	diarrhea: 6.9% vomiting: 1.4% abd pain: 0% nausea: 3.4%	11 withdrawals total study, # due to AE unclear	
Weippl 1993[77] (93) Pharyngitis	10mg/kg qd	30-50mg/kg in 3 divided doses	3 days	10 days	5.4 NR	5.0 NR	11% NR	13% NR	8.7% NR	13% NR	0% NS	2.1% NS

Clarithromycin vs azithromycin

Eleven trials reported adverse events in head-to-head studies of clarithromycin vs azithromycin.[24, 25, 37, 55-57, 67, 68, 76, 94, 95] No significant differences are reported in adverse event rates. A single study reported a higher discontinuation rate for azithromycin versus clarithromycin.[56] No consistent trend in adverse events was observed.

Table 21. Adverse events - azithromycin vs clarithromycin

Trial (n) Indication	Treatment		Duration (days)		Mean age (yr) % male		All AE		GI AE		Withdrawals	
	Azi	Clari	Azi	Clari	Azi	Clari	Azi	Clari	Azi	Clari	Azi	Clari
Arguedas, 1997[67] (97) AOM	10 mg/kg/day QD	15 mg/kg/day (BID)	3 days	10 days	4.17 48.5 %	4.2 48.5 %	18% NS	31.9 % NS	10% NS	21.3% NS	0% NS	2.1% NS

Table 21. Adverse events - azithromycin vs clarithromycin (continued)

Trial (n) Indication	Treatment		Duration (days)		Mean age (yr) % male		All AE		GI AE		Withdrawals	
	Azi	Clari	Azi	Clari	Azi	Clari	Azi	Clari	Azi	Clari	Azi	Clari
Muller, 1993[37] (380) AOM/Sinus-titis/ Pharyngitis	500 mg QD	250 mg BID	3 days	10 days	39.7 59.5 %	59.5 59.5 %	8% NR	7.4% NR	7.3% NR	5.3% NR	1.6% NR	1.6% NR
Sopena, 2004[24] (70) CAP	azi 500mg po QD*	clari 250mg BID	3 days	10-14 days	41.7 NR	44.4 NR	26.5 % azi NR	25% clari NR	NR		NR	
O'Doherty 1998[25] (n=203) CAP	azi 500mg po QD	clari 250mg BID	3 days	10 days	50.1 60%	51.5 58%	14% p=.81 5	13% p=.81 5	7% NR	8% NR	Total: 1% Due to AEs: 0% NS	Total: 4% Due to AEs: 2% clari NS
Swanson, 2005[56] (322) AECB/ABEC B	500 mg QD	500 mg BID	3 days	10 days	61.4 62.1 %	57.9 i 62.1 %	20.9 % NS	26.8 % NS	diarrhea 4.4% nausea 4.4% abd pain 6.3% NR	diarrhea 5.5% nausea 3.7% abd pain 6.1% NR	0% p<0.05	3% p<0.05
Bradbury, 1993[55] (510) AECB/ABEC B	500 mg QD	250 mg BID	3 days	10 days	55.9 58.8 % M		9% NS	6% NS	6% NS	3.9% NS	0.4% NS i	1.2% NS
Venuta 1998[76] (174) Pharyngitis	10mg/ kg	7.5mg/ kg BID	3 days	10 days	7.91 47% M		5.4% NS	4.8% NS	5.4% NS	4.7% NS	0% for both interventions	
Dunne 2000[94] (239) MAC tx	250 mg qd and 600 mg qd	500 mg bid	Varied up to 24 weeks		36 (250 mg) 38 (600 mg) 86.2 %	37 clari 86.2 %	NR (250 mg) 60% (600 mg) NS	65% NS	NR		NR (250mg) 9% azi (600mg)	5.8% NS
Ward 1998[95] (59) MAC tx	600 mg qd	500 mg bid	Varied up to 16 weeks		NR		29% NS	29% NS	NR		8% NS	9% NS
Pozzi, 1994[57] (205) AECB/ABEC B	500 mg QD	250 mg BID	3 days	7 days	63.9 83.8 % M	65.4 83.8 % M	3.9% NR	0% NR	2.9% NR	0% NR	0% for both interventions	
Ramet, 1995[104] (150) AOM	10 mg/kg x 1, 5 mg/kg x 4	7.5 mg/kg BID	5 days		1.9 58.8 % M	2.0 58.8 % M	14.5 % NR	13.5 % NR	6.6% NR	5.4% NR	0% NR	2.7% NR

Clarithromycin IR vs Clarithromycin ER

No significant differences in adverse events were reported in any of the 5 trials comparing clarithromycin formulations.[38, 58-61]

Table 22. Adverse events – clarithromycin IR vs clarithromycin ER

Trial (n) Indication	Treatment		Duration (days)		Mean age % male		All adverse events		Gastrointestinal adverse events		Withdrawals	
	IR	ER	IR	ER	IR	ER	IR	ER	IR	ER	IR	ER
Adler, 2000[58] (620) AECB/ABECB	500 mg BID	1000 mg QD	7 for both		54.6 43.5 % M	54.3 43.5 % M	17% NS	22% NS	diarrhea 4% nausea 3% NS	diarrhea 6% nausea 3% NS	3% NS	2.8% NS
Gotfried, 2005[59] (485) AECB/ABECB	500 mg BID	1000 mg QD	7 days	5 days	61.6 48.5 %	62.1 48.5 %	18% NS	13% NS	11% NS	8% NS	1.6% NS	2.5% NS
Nalepa, 2003[60] (703) AECB/ABECB	250 mg BID	500 mg QD	5 for both		57.4 60.5 %	58.1 60.5 %	5% NS	7% NS	diarrhea 1% NS	diarrhea 2% NS	0.3% for both NS	
Weiss, 2002[61] (230) AECB/ABECB	250 mg BID	500 mg QD	7 for both		59.6 45.1 % M	59.9 45.1 % M	62.9% NS	67.5% NS	NR		0.9% NS	3.4% NS
Murray 2000[38] (283) Sinusitis	500 mg BID	1000 mg QD	14 for both		41.0 36.4 %	41.9 36.4 %	28% p=0.60	32% p=0.60	diarrhea 8% nausea 9%	diarrhea 6% nausea 5%	8% p=0.13	4% p=0.13

Indirect Comparisons

Overall adverse event rates varied from 4-36% with azithromycin; 4-58% with clarithromycin; and 2-100% with erythromycin. An additional 54 active controlled trials reported adverse events without available rates. No conclusions can be drawn from these studies about the relative safety and adverse event rates among the macrolides.

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities, or in pregnancy for which one macrolide is more efficacious or associated with fewer adverse events?

Age, Race, Gender

Age in trials of adults ranged from a mean of 22 to 61.9 years. Few trials reported subgroup analysis of the influence of age on efficacy and no trial reported subgroup analysis of adverse events. Of the 54 trials evaluated, six trials did not report age[29, 33, 44, 55, 71, 95]. A comparative study of clarithromycin and erythromycin evaluated patients under and over the age of 65 with no difference in efficacy against streptylococcal pharyngitis observed between these age groups.[75] Three trials of immediate vs. extended release clarithromycin in the treatment of AECB/ABECB reported subgroup analyses that included age.[58, 59, 61] In each of these trials, subgroup analyses were reported for each antibiotic regimen, and no statistically significant differences in response rates were noted in the 2 comparator arms.

Pediatric patients were studied in 11 trials of CAP, AOM, and streptococcal pharyngitis; ages ranged from a mean of 0.58 yr - 11.58 yr.[27-29, 33, 69, 70, 72, 73, 76, 77, 105]. In CAP trials, the definitions of pediatric were variable, ranging from 3-12y, 6mos-16y, 1mo-14y, and 5-16y.[27-29, 33] The majority of studies did not perform subgroup analysis for efficacy or adverse events based on demographic data. One study comparing erythromycin estolate to amoxicillin in AOM reported clinical responses in relation to age 24 months or younger versus older than 24 months, but these results were not separately reported for the 2 treatment arms.[73]

When clinical outcomes are compared between adult trials and pediatric trials in CAP, AOM, and streptococcal pharyngitis, no conclusions can be drawn based on the variability of response within age subgroups between studies. Overall clinical cure rates ranged from 53% to 92% (AOM 74%-79%; CAP 53-69%; pharyngitis 80-92%) in the adult studies and 37-100% (AOM 37-100%; CAP 76-100%; pharyngitis 80-92%) in the pediatric studies.

Race was reported in 24[27, 29, 30, 32, 33, 36, 38, 41, 45, 56, 58-62, 65, 66, 72, 76, 99-101, 106, 107] of 54 trials. While the majority of patients were Caucasian/white in the studies, the range was 13-99%. Only two trials, comparing immediate vs. extended release clarithromycin in the treatment of AECB/ABECB, reported subgroup analyses that included race.[58, 59] In each of these trials, subgroup analyses were reported for each antibiotic regimen, and no statistically significant differences in response rates were noted in the 2 comparator arms. No study reported subgroup analysis of adverse events based on race. The exception is a trial of CAP comparing azithromycin and erythromycin in pediatric patients, which had an African American majority (53%).[29] Presentation of the data do not allow comparisons within this study of effects of race, nor can the study be compared to other trials of primarily Caucasian populations. The data are insufficient to determine whether differences exist among macrolides based on race.

Only two trials, comparing immediate vs. extended release clarithromycin in the treatment of AECB/ABECB, reported subgroup analyses that included gender.[58, 59] In each of these trials, subgroup analyses were reported for each antibiotic regimen, and no statistically significant differences in response rates were noted in the 2 comparator arms. The data are insufficient to determine whether any difference exists in response to individual macrolides based on gender.

Drug-Drug Interactions (Head to Head Trials)

Drug-drug interactions must be taken into account when considering macrolide therapy. These interactions cannot be addressed with the efficacy studies in this report as patients taking drugs known to have significant interaction with macrolides were excluded in many of the trials reviewed.[24, 25, 27, 29, 36, 38-40, 42, 45, 48, 49, 56, 58, 60, 75, 77, 101, 106-108] The macrolides have variable degrees of inhibition of cytochrome P450-3A4 (CYP3A4) and are also substrates of this enzyme. The use of macrolides with other drugs metabolized by CYP3A4 may result in increases in the concentrations of the second drug. Erythromycin is the most potent inhibitor of CYP3A4, followed by moderate inhibition with clarithromycin, and and little to no inhibition by azithromycin.[109] Erythromycin has been implicated in interactions with multiple drugs, including: benzodiazepines, carbamazepine, cyclosporine, digoxin, HMG-CoA inhibitors, tacrolimus, and theophylline. Case reports of interactions with warfarin have been documented for many of the macrolides.[110] Clarithromycin, though in vitro a less potent inhibitor of CYP3A4, has been associated with a similar scope of clinical interactions.[110] As expected by its limited CYP activity, few clinically important interactions have been reported with azithromycin.[110,112]

Pregnancy

Erythromycin and azithromycin are pregnancy Category B; clarithromycin is pregnancy Category C. Pregnant patients were explicitly excluded from the majority of the head-to-head trials. Further, no studies reported enrollment of pregnant patients.

SUMMARY

Table 23 summarizes the evidence contained in this report:

Table 23. Summary of evidence

Key Question	Overall level of evidence	Conclusion
Key Question 1. For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and *Mycobacterium Avium* complex, do macrolide antibiotics differ in efficacy?		
	Direct comparisons	
	CAP: Fair, but limited	*Adults: Differences in clinical cure rates were not found. Limited evidence is available for consideration of differences.* *Children: Clinical cure rates were similar and ranged from 76-100% in the studies.*
	Sinusitis: Fair	*Adults: Differences in clinical and bacteriologic cure rates were not found.* *Children: Data were insufficient to compare macrolides.*
	AECB/ABECB: Fair	*Adults: Differences in clinical cure rates were not found.* *With the exception of a statistically significant difference in microbiologic response rate in favor of azithromycin in one trial, differences in bacteriologic cure rates were not found* *Children: No appropriate trials of AECB/ABECB in children were identified in the literature search.*
	Otitis: Fair, but limited	*Adults: The sole head-to-head trial comparing azithromycin to clarithromycin found no significant differences in either cure or improvement.* *Children: In 2 fair-quality head-to-head trials of azithromycin and clarithromycin no statistically significant differences in clinical response were noted. Microbiologic outcomes were not assessed.*
	Pharyngitis: Fair	*Adults: No differences in clinical cure were observed in direct comparisons of clarithromycin with either azithromycin or erythromycin.* *Children: No differences in clinical cure were observed in direct comparisons of azithromycin with clarithromycin. A single study of azithromycin vs erythromycin reported a higher clinical cure rate for azithromycin but no difference was observed in clinical response when defined as cure/improvement.*

Table 23. Summary of evidence (continued)

Key Question	Overall level of evidence	Conclusion
	MAC: Fair	*Adults: There were no direct comparison trials identified in the literature search examining the use of azithromycin or clarithromycin in the prophylaxis of MAC infection in HIV-infected patients.* *Evidence of the comparative efficacy of azithromycin and clarithromycin was somewhat inconsistent across the only two head-to-head trials identified for the treatment of MAC infection. However, the available evidence tends to favor clarithromycin for the treatment of MAC infection.* *Children: No clinical trials examining macrolide use in HIV-infected children either for treatment or prophylaxis of MAC infection were identified.*
	Indirect comparisons: Fair	*Evidence from active-controlled trials comparing a macrolide to penicillin, amoxicillin, amoxicillin/clavulanic acid or dirithromycin found similar clinical and microbiological cure rates across all indications and comparisons.* *Placebo controlled studies were limited and provided no additional information.*
Key Question 2: For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and *Mycobacterium Avium* complex, do macrolide antibiotics differ in safety or adverse events?	Direct comparisons: Fair Indirect comparisons: Poor	*Erythromycin was associated with higher overall and GI adverse event rates and withdrawals due to adverse events than clarithromycin in the majority of the available studies.* *No significant differences in adverse event rates were observed between clarithromycin (both IR and ER) and azithromycin.* *Indirect comparisons: No conclusions about the relative safety and adverse event rates among the macrolides can be drawn from either the active- or placebo-controlled trials.*
Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities, or in pregnancy for which one macrolide is more efficacious or associated with fewer adverse events?	Poor	*No evidence is available to suggest that one macrolide is more efficacious or associated with fewer adverse events when used in any subgroup (including race, gender, concomitant medication use and pregnancy) for any of the studied indications.*

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Appendix A. Search strategies

Ovid MEDLINE - bronchitis
Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 azithromycin$.mp. or AZITHROMYCIN/ (2789)
2 erythromycin$.mp. or ERYTHROMYCIN/ (15982)
3 clarithromycin$.mp. or CLARITHROMYCIN/ (4683)
4 1 or 2 or 3 (21131)
5 bronchitis.mp. or exp BRONCHITIS/ (25276)
6 4 and 5 (525)
7 limit 6 to (humans and english language) (354)
8 from 7 keep 1-354 (354)

Ovid MEDLINE – Community acquired pneumonia
Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 azithromycin$.mp. or AZITHROMYCIN/ (2789)
2 erythromycin$.mp. or ERYTHROMYCIN/ (15982)
3 clarithromycin$.mp. or CLARITHROMYCIN/ (4683)
4 1 or 2 or 3 (21131)
5 exp Community-Acquired Infections/ (3781)
6 exp PNEUMONIA/ (47833)
7 5 and 6 (2188)
8 4 and 7 (204)
9 (community acquir$ adj5 pneumon$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2985)
10 4 and 9 (376)
11 8 or 10 (398)
12 limit 11 to (humans and english language) (325)
13 from 12 keep 1-325 (325)

Ovid MEDLINE – Mycobacterium avium complex
Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 azithromycin$.mp. or AZITHROMYCIN/ (2789)
2 erythromycin$.mp. or ERYTHROMYCIN/ (15982)
3 clarithromycin$.mp. or CLARITHROMYCIN/ (4683)
4 1 or 2 or 3 (21131)
5 maic.mp. or exp Mycobacterium avium Complex/ (1553)
6 exp Mycobacterium avium-intracellulare Infection/ (2068)
7 exp Mycobacterium avium/ (1856)

8 exp Bacterial Infections/ (444752)
9 7 and 8 (1029)
10 5 or 6 or 9 (3671)
11 4 and 10 (463)
12 limit 11 to (humans and english language) (356)
13 from 12 keep 1-356 (356)

Ovid MEDLINE – Otitis media
Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 azithromycin$.mp. or AZITHROMYCIN/ (2789)
2 erythromycin$.mp. or ERYTHROMYCIN/ (15982)
3 clarithromycin$.mp. or CLARITHROMYCIN/ (4683)
4 1 or 2 or 3 (21131)
5 otitis media.mp. or exp Otitis Media/ (17367)
6 4 and 5 (386)
7 limit 6 to (humans and english language) (300)
8 from 7 keep 1-300 (300)

Ovid MEDLINE – pharyngitis
Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 azithromycin$.mp. or AZITHROMYCIN/ (2789)
2 erythromycin$.mp. or ERYTHROMYCIN/ (15982)
3 clarithromycin$.mp. or CLARITHROMYCIN/ (4683)
4 1 or 2 or 3 (21131)
5 pharyngiti$.mp. or exp PHARYNGITIS/ (5845)
6 4 and 5 (361)
7 limit 6 to (humans and english language) (293)
8 from 7 keep 1-293 (293)
9 from 8 keep 1-293 (293)

Ovid MEDLINE – sinusitis
Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 azithromycin$.mp. or AZITHROMYCIN/ (2789)
2 erythromycin$.mp. or ERYTHROMYCIN/ (15982)
3 clarithromycin$.mp. or CLARITHROMYCIN/ (4683)
4 1 or 2 or 3 (21131)
5 exp SINUSITIS/ or sinusiti$.mp. (12097)
6 sinus infection$.mp. (283)
7 5 or 6 (12194)
8 4 and 7 (278)

9 limit 8 to (humans and english language) (212)
10 from 9 keep 1-212 (212)

Cochrane Central Register of Controlled Trials – for all indications
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2006>
Search Strategy:
---
1 (erythromycin or clarithromycin or azithromycin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2915)
2 macrolide$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (437)
3 (cap or "community acquired pneumonia").mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (768)
4 otitis media.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1317)
5 sinusitis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (777)
6 bronchitis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2055)
7 pharyngitis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (834)
8 mycobacterium avium complex.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (102)
9 3 or 4 or 5 or 6 or 7 or 8 (5563)
10 1 or 2 (3060)
11 9 and 10 (646)

Cochrane Database of Systematic Reviews – for all indications
Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2006>
Search Strategy:
---
1 (erythromycin or clarithromycin or azithromycin).mp. [mp=title, abstract, full text, keywords, caption text] (110)
2 macrolide$.mp. [mp=title, abstract, full text, keywords, caption text] (58)
3 (cap or "community acquired pneumonia").mp. [mp=title, abstract, full text, keywords, caption text] (69)
4 otitis media.mp. [mp=title, abstract, full text, keywords, caption text] (78)
5 sinusitis.mp. [mp=title, abstract, full text, keywords, caption text] (55)
6 bronchitis.mp. [mp=title, abstract, full text, keywords, caption text] (139)
7 pharyngitis.mp. [mp=title, abstract, full text, keywords, caption text] (51)
8 mycobacterium avium complex.mp. [mp=title, abstract, full text, keywords, caption text] (0)
9 3 or 4 or 5 or 6 or 7 or 8 (291)
10 1 or 2 (127)
11 9 and 10 (46)

Appendix B. Quality criteria

The purpose of this document is to outline the methods used to produce this drug class reviews for the Washington State Prescription Drug Program.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random numbers tables

   Inferior approaches to sequence generation:
   - Use of alteration, case record numbers, birth dates or week days
   - Not reported

2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization:
   - Centralized or pharmacy-controlled randomization
   - Serially-numbered identical containers
   - On-site computer based system with a randomization sequence that is not readable until allocation
   - Other approaches sequence to clinicians and patients

   Inferior approaches to concealment of randomization:
   - Use of alteration, case record numbers, birth dates or week days
   - Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

<u>Assessment of External Validity (Generalizability)</u>

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

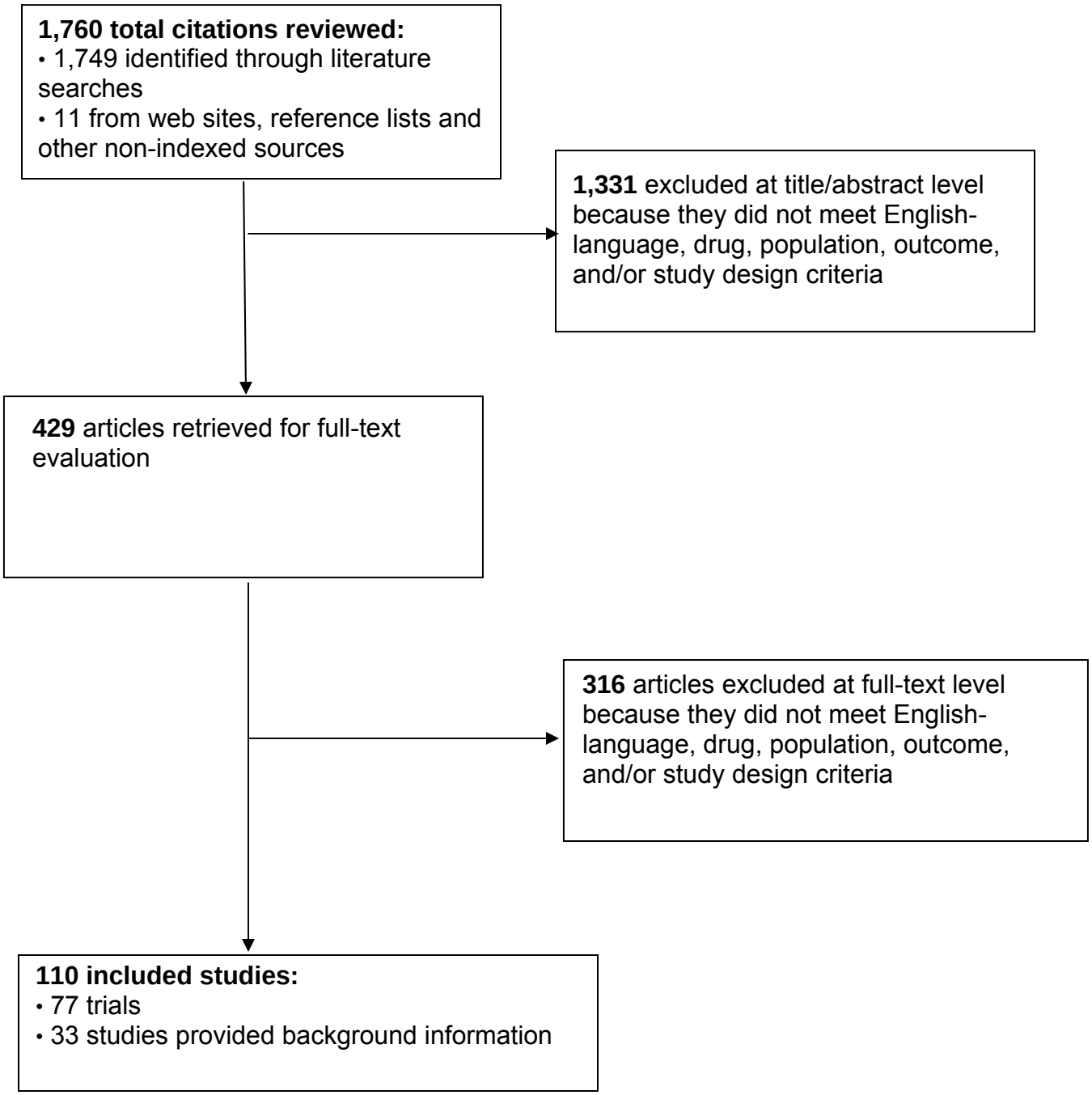
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up?

Appendix C. Results of literature search



Appendix D. Listing of abbreviations

a/c; amox/clav - *amoxicillin + clavulanic acid*
AEs: *adverse events*
azi - *azithromycin*
amox - *amoxicillin*
BID - *2 times daily*
clari - *clarithromycin*
diri - *dirithromycin*
ery - *erythromycin*
ITT - *intention-to-treat*
NR - *not reported*
NS- *not significant*
QD - *once daily*
rifa - *rifabutin*
TID - *3 times daily*